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Abstract: Residency at high altitude (HA) demands adaptation to challenging environmental conditions with hypobaric hypoxia being the most important one. Epidemiological and experimental data suggest that chronic exposure to HA reduces cancer mortality and lowers prevalence of metabolic disorders like diabetes and obesity implying that adaption to HA modifies a broad spectrum of physiological, metabolic and cellular programs with a generally beneficial outcome for humans. However, the complexity of multiple, potentially tumor-suppressive pathways at HA impedes the understanding of mechanisms leading to reduced cancer mortality. Many adaptive processes at HA are tightly interconnected and thus it cannot be ruled out that the entirety or at least some of the HA-related alterations act in concert to reduce cancer mortality. In this review we discuss tumor formation as a concept of competition between healthy and cancer cells with improved fitness - and therefore higher competitiveness - of healthy cells at high altitude. We discuss HA-related changes in glucose, lipid and iron metabolism that may have an impact on tumorigenesis. Additionally, we discuss two parameters with a strong impact on tumorigenesis, namely drug metabolism and physical activity, to underpin their potential contribution to HA-dependent reduced cancer mortality. Future studies are needed to unravel why cancer mortality is reduced at HA and how this knowledge might be used to prevent and to treat cancer patients.

DOI: https://doi.org/10.1016/j.yexcr.2017.03.048

Reduced Cancer Mortality at High Altitude: The Role of Glucose, Lipids, Iron and Physical Activity

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Abstract

Residency at high altitude (HA) demands adaptation to challenging environmental conditions with hypobaric hypoxia being the most important one. Epidemiological and experimental data suggest that chronic exposure to HA reduces cancer mortality and lowers prevalence of metabolic disorders like diabetes and obesity implying that adaption to HA modifies a broad spectrum of physiological, metabolic and cellular programs with a generally beneficial outcome for humans. However, the complexity of multiple, potentially tumor-suppressive pathways at HA impedes the understanding of mechanisms leading to reduced cancer mortality. Many adaptive processes at HA are tightly interconnected and thus it cannot be ruled out that the entirety or at least some of the HA-related alterations act in concert to reduce cancer mortality. In this review we discuss tumor formation as a concept of competition between healthy and cancer cells with improved fitness – and therefore higher competitiveness – of healthy cells at high altitude. We discuss HA-related changes in glucose, lipid and iron metabolism that may have an impact on tumorigenesis. Additionally, we discuss two parameters with a strong impact on tumorigenesis, namely drug metabolism and physical activity, to underpin their potential contribution to HA-dependent reduced cancer mortality. Future studies are needed to unravel why cancer mortality is reduced at HA and how this knowledge might be used to prevent and to treat cancer patients.

1 Introduction

Humans living at moderate (above 1500 m) and high (above 2500 m) altitude (HA) are chronically exposed to hypobaric hypoxia and need to adapt to this environmental challenge. The altitude-dependent drop in barometric pressure and subsequent decrease of the ambient partial pressure causes hypoxemia and tissue hypoxia. When sojourners acclimatize, their bodies respond first with short-term adaptations (hours to days; e.g. increased basal ventilation [1], plasma volume reduction [2, 3]) and later with long-term adaptations (weeks to months; e.g. increased erythropoiesis [4]) that are mainly driven by tissue hypoxia. The magnitude of response to HA is the key factor for physiological adaption or pathological mal-adaption, the latter resulting in hypoxia-related altitude illnesses [5-7]. The cellular response to hypoxia is driven by hypoxia inducible transcription factors (HIF) that are rapidly activated when intracellular oxygen levels decline [8-10]. Iron-dependent prolyl-hydroxylases (PHDs) regulate the stability of HIF-α subunits resulting in either protein degradation when oxygen is sufficiently available or stabilization when oxygen supply is low [11]. The detailed regulation of HIFs by oxygen availability and their down stream targets have been extensively reviewed [11-13]. During oxygen deficiency, hematopoiesis is driven by the renal hormone erythropoietin (Epo) that is oxygen-dependently regulated by HIF-2 [14] and promotes red blood cell production.

Epidemiological studies provide evidence that humans populating high altitude environments show reduced cancer mortality. Several possible explanations have been discussed in the past including elevated vitamin D synthesis due to higher background radiation [15]. However, the most adaptive processes at HA occur in response to reduced oxygen availability and this might be a much greater factor in cancer mortality. At the first glance, the observation of oxygen-dependent reduced cancer mortality at HA is counterintuitive because tumor hypoxia *per se* is rather a supportive factor for tumor growth and the development of aggressive phenotypes [16, 17]. Both hypoxia-inducible factors 1 and 2 (HIF-1/2) have been reported to promote tumor growth and metastasis [18-20]. In contrast, some studies show that the loss of HIF-1α expression promotes kidney cancer [21] suggesting that at least in some tissues

stabilized HIF is tumor suppressive. Recent studies analyzed evolutionary selected variants *EGLN1* (encoding for PHD2) and *EPAS1* (encoding for HIF-2α) genes in Tibetans and reported association of these variants with increased lung [22] and gastric [23] cancer risk. These HA-adapted variants of *EGLN1* with D4E and C127S polymorphisms increased PHD2 activity and promote HIF-α degradation [24, 25] suggesting that HIF stabilization at HA might contribute to reduced incidence/mortality of at least some types of cancer. In this review we briefly summarize the results of epidemiological and animal studies and discuss mainly oxygen-based mechanisms that may account for reduced cancer mortality. It should be mentioned that "mortality" is a clinical relevant outcome but does not further explain at which steps during the course of cancer disease (incidence, progression, dissemination, response to therapy) exposure to HA has affected and altered.

2 Epidemiology

2.1 Human Studies

In 1974/75 an inverse relationship of HA and leukemia cancer mortality in humans was reported for the first time [26-28]. These studies were followed by additional studies within the last decades that considered potential cofounders (such as environment and socio-economic status) and confirmed these findings [29-35]. Although overall cancer mortality negatively correlates with HA [31], site-specific cancer seem to respond differently to HA. While lymphoma, breast [36], lung, cancers of tongue and mouth or larynx [29, 35] display reduced mortality at HA, liver and cervix mortality showed no difference between low and high altitude. As expected, mortality from melanoma was increased due to the higher background radiation [37]. Very recently, it has been shown that highlanders display a reduced incidence of lung and breast cancer [38] supporting earlier observations that HA is indeed involved in prevention of tumorigenesis.

2.2 Animal Studies

Reduced cancer mortality at HA is not unique to humans but has been observed in mice exposed to very high altitude (4540 m) for a prolonged period of time after exposure to sub-

lethal levels of x-rays resulting in reduced incidence of tumor formation [39]. Additionally, the incidence of spontaneous leukemia is reduced at HA [40] but spontaneously forming pulmonary tumors display a higher incidence at HA [41]. Back in the 1980s, studies in several rat and mouse tumor models demonstrated reduced primary tumor growth and metastatic spread as well as improved response to therapeutic treatment at HA [42-44]. A more recent study showed reduced tumor incidence not only in two spontaneously developing tumor mouse models, namely $p53^{-/-}$ and $APC^{Min/+}$, but also in a chemically induced skin cancer model in mice exposed to 10% normobaric oxygen [45] corresponding to an extreme altitude of approximately 5500 – 6000 meter above sea level [12]. With their experimental setup, the latter authors prove that reduced oxygen levels protect from oncogenic events and tumorigenesis matching the epidemiological findings of Simeonov and Himmelstein [38].

3 Cancer and Adaptation

Theoretically, cancer cells can be considered to be evolutionary selected cell lineages that have escaped control of replication and cell death and meet the traditional characteristics of minimal Darwinian populations, namely variation, selection and inheritance [46]. As a consequence, the evolutionary process of tumor formation, progression and metastasis depends on the nature of the niche that is populated by cancer cells and their ability to compete for resources with healthy cells within the same niche. Natural selection demands genotypes that differ in fitness to result in improved reproduction success. Although oncogenic events are commonly assumed to increase cellular fitness, DeGregori, (2011) suggests a model of adaptive oncogenesis, in which genetic variations rarely result in advantageous traits in healthy (and young) populations of (stem) cells, since they always display a high degree of fitness to maintain tissue integrity and this successfully competes against somatic cancer cell evolution [47]. Cell age and/or damaging insults reduce cellular fitness and change the adaptive landscape due to accumulation of mutations and alterations in the microenvironment, both promoting selection of adaptive oncogenesis events [47]. An example in relation to cancer at HA is melanoma that is increased due to increased radiation exposure [37] resulting in increased damage of epidermal cells and consequently the reduction in cell fitness. In the light of this hypothesis, we discuss below reduced cancer

mortality and incidence at HA as a competitive mechanism between cancer and healthy cells. We suggest that HA increases fitness of healthy cells and/or modifies the tumor microenvironment resulting in adverse conditions for tumor cell development and expansion. Other diseases (e.g. stroke and cardiovascular diseases) display also a link between high altitude and reduced mortality [48] supporting our assumption. As a matter of fact, the metabolic syndrome, diabetes type 2 and obesity are cancer risk factors [49, 50] and have a lower prevalence in humans populating elevated areas [51-53]. In the next sections, we consider cell biological and metabolic alterations at HA that might pose a bottleneck for emerging tumors in humans living at higher elevations.

3.1 Metabolic Alterations

3.1.1 Glucose and Glutamine Metabolism

The competition for nutrition in a resource-restricted environment may result in different metabolic pathways being susceptible to alterations that might occur at HA. The most prominent metabolic reprogramming in tumor cells is the “Warburg effect” resulting in aerobic metabolism of glucose and increased lactate production – even when sufficient oxygen is available [54]. A recent review summarizing tumor metabolism and discussing metabolites that limit tumor progression as potential therapeutic targets suggested that neither ATP nor NADPH may limit tumor proliferation [54]. However, restoration of tricarboxylic acid (TCA) cycle metabolites and the synthesis of nucleotides may be a limiting factor in tumor progression due to the high demand for DNA synthesis in proliferating cells. Glucose and/or glutamine (depending on tumor type and microenvironment) refuel the TCA cycle and provide substrates for the nucleotide metabolism [55, 56]. Consequently, both, glucose and glutamine may limit tumor progression when insufficiently supplied to cancer cells (e.g. when healthy cells increase their demand, or when less substrate is provided from blood). As expected, hyperglycemia correlates with an increased risk of tumorigenesis [57] and because highlanders have reduced plasma glucose and glutamine concentrations (at least in acute and prolonged exposure to HA [58, 59]) this restriction possibly contributes to reduced cancer mortality [58, 60]. Blood glucose levels are mainly controlled by the liver and partially by kidneys [61, 62] and release of hepatic glucose is stimulated by glucagon, fatty acids and

catecholamines but suppressed by insulin [61]. Accordingly, as Andean highlanders display higher glucagonemia and lower glycemia, their exposure to HA might reduce hepatic glucagon sensitivity resulting in reduced glucose release from the liver. In cancer cells, HIF-1 increases the expression levels of glucose transporter 1 and 3 (GLUT1/3) to facilitate glucose uptake [63]. However, adipocytes respond similarly to hypoxia with increased GLUT1/3 expression levels [64]. Furthermore, acclimatization to HA increases the uptake and metabolism of blood glucose by human skeletal and heart muscle [61], facilitated by a hypoxia-driven increase in HIF-1 as well as GLUT4 expression levels in human muscle cells [61, 65].

In conclusion, cancer cells are competing with healthy cells and tissues (e.g. muscles) for nutrition including glucose and glutamine and exposure to HA possibly limits the availability (reduced plasma levels) and increases glucose uptake and metabolism in healthy tissue (competition) for these metabolites. However, metabolic pathways are intricately interconnected and many cancer cells utilize a broad spectrum of metabolites including lipids, lactate and further amino acids [54] potentially compensating reduced availability of even central substrates like glucose.

3.1.2 Lipid Metabolism

Lipid metabolism is a complex process that is regulated by multiple pathways to control uptake, transport, metabolism and synthesis. In turn, lipids also differentially regulate cellular signaling transduction and pathways [66]. The cell membrane, mainly consisting of lipids, contains lipid rafts that are spatial membrane assemblies of cholesterol and derivatives providing a platform for signaling transduction processes involved in apoptosis [67] as well as cell survival and proliferation [68, 69]. Small variations in the tightly regulated metabolism of lipids result in disturbed energy homeostasis ultimately leading to fat accumulation, increased body mass and obesity, which are risk factors for breast [70], colon [71], kidney [72], prostate [73], gallbladder [74] and pancreas cancer [75]. Fast growing tumors display dysregulated lipid homeostasis with reduced 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase and low-density lipoprotein (LDL) receptor activity as well as cholesterol enrichment in tumor cells [76]. Cancer cells require energy as well as metabolic precursors for cell proliferation associated with rapid lipid synthesis for assembling membranes of new cells. Lipids are

provided from external sources as well as intracellularly by fatty acid synthesis [76] and regulate, besides membrane assembly, the cancer related pathways PI3K/AKT/mTOR, RAS and Wnt [76-78]. Further, free fatty acids in human plasma are also involved in insulin resistance [79] resulting in high insulin and insulin-like growth factors (IGF) that directly promote tumor progression [73, 76]. The lipid profile of tumors in patients at HA has not been published, but hypoxia has been shown to facilitate exogenous lipid uptake of cancer cells [80, 81]. Such a lipid supply might be suppressed in highlanders who have been reported to exhibit lower fatty acid plasma levels [61] and potentially decrease fatty acid metabolism due to SIRT4 induction [82]. Elevated lipid levels are commonly accepted to be severe risk factors for cancer [83, 84]. Highlanders living at moderate altitude (1500 m) have reduced levels of total cholesterol and triglycerides but an increase of high density lipoprotein (HDL) [85, 86] that correlates with reduced prevalence of both cardiovascular diseases [87, 88] and cancer incidence including breast [89], prostate [90, 91] and potentially colon cancer, as shown in mice [92]. Collectively, the restricted lipid metabolism at HA might be shifted against the development and progression of tumors.

3.1.3 Iron Metabolism and Anemia of Cancer

Iron is an essential nutrient involved in the formation of red blood cells, in many oxidation-reduction processes within the organism as well as in energy metabolism, mitochondrial respiration, and DNA synthesis. Iron metabolism is controlled on both the systemic and cellular levels. The liver hormone hepcidin is a key regulator for iron homeostasis inhibiting intestinal iron absorption as well as macrophage release by degrading the iron-transport protein ferroportin (Fpn1) [93-95]. Hypoxia is tightly associated with iron metabolism. HIFs control directly or indirectly the expression of the divalent metal transporter 1 (DMT-1) and Fpn1 among others [96, 97] and iron is an essential cofactor for PHDs that catalyze the hydroxylation of HIF-α subunits to target them for degradation [11-13]. Under hypoxic conditions hepcidin mRNA transcription is indirectly inhibited by Epo via erythroferrone [96, 98] to guarantee sufficient iron supply for red blood cell formation. Cancer cells have a higher iron demand and thus elevated iron uptake. Correspondingly, high iron levels have been determined as a risk factor for cancer [99-101] with an impact on tumor-associated macrophages and the tumor microenvironment [102]. Cancer cells display disturbed iron

homeostasis with increased expression of transferrin receptor 1 (uptake) [103], decreased expression of ferritin (storage) [104, 105] and inhibition of ferroportin (release) [106]. Exposure to HA demands increased hematopoiesis to cope with reduced oxygen uptake and thus is associated with elevated iron utilization for red blood cell formation [96]. At very high altitudes female adults develop reduced body iron levels [107] potentially decreasing the risk for tumor incidence. Acute or short-term exposure to HA decreases plasma iron levels, ferritin and transferrin saturation depending on the dietary iron intake [108, 109]. The critical role of iron in malignancy has been demonstrated by use of iron chelators that sequester iron or by applying antibodies against the transferrin receptor 1 [110-112]. Both approaches inhibit cancer progression. Iron deficiency is the most prevalent nutritional disorder [113] resulting in anemia. This includes anemia of cancer [114] that frequently occurs in patients secondary to their cancer [114] or is induced during chemo and/or radiotherapy [115, 116]. Anemia of cancer reduces quality of life and is a poor prognostic factor in cancer patients [117, 118]. Consequently, it demands treatment that is currently achieved by iron supplementation, administration of erythropoiesis-stimulating agents (ESA) and blood transfusion [114]. Hepcidin expression (the aforementioned key regulator of iron homeostasis) is frequently induced in tumor patients by cancer-induced inflammatory signals [119] and prevents iron uptake resulting in iron deficiency and finally anemia. Interestingly, hepcidin levels – at least during acute and prolonged exposure to HA and isobaric hypoxia – decline to meet the increased iron demand [120-123]. Epidemiological data on hepcidin expression levels and anemia of cancer in highlanders are missing and, consequently, thorough reports on frequency, severity and treatment success are required to determine its role in cancer mortality at HA. It has been reported, however, that the frequency of end-stage renal disease dependent anemia (which can occur in cancer patients as a result of renal tumor invasion [114]) is reduced [124, 125]. Additionally, the response to Epo or erythropoiesis-stimulating agents (ESA) is improved at HA [126, 127]. Besides iron deficiency, impaired Epo production (due to cancer- or therapy-induced kidney damage) is the major cause for anemia of cancer [114]. With increasing altitude the number of end-stage renal disease patients receiving ESA as well as the required dosages surprisingly are lower while hemoglobin levels as well as patient survival are higher [126, 127]. The reduced requirement of ESA treatment in anemic

patients at HA may also have implications for cancer mortality. Several clinical [128-135] and preclinical [136-144] studies suggest that ESA treatment in cancer patients actually reduces patient survival by promoting tumor growth via binding to Epo receptors on many cancer cell types. Hence, the FDA has lowered the minimally accepted hemoglobin levels in anemic cancer patients (lowlanders) to <12 g/dl [145, 146]. A potentially lower demand of ESA to treat anemia of cancer at HA might thus contribute to reduced cancer mortality at HA.

3.2 Pharmacokinetics and Pharmacodynamics at HA

A frequently ignored subject is the alteration of drug metabolism at HA. In addition to surgery and irradiation, chemotherapy is the most frequent choice of treatment in cancer. The pharmacokinetic and pharmacodynamic responses to drugs have been poorly studied in highlanders [147]. With respect to the approximately 400 million humans living at elevated areas (above 1500 m) [48, 148], this population is considerably underrepresented, especially because there is clear evidence that HA exposure (like all other physiological stress conditions) has impact on drug absorption, distribution, metabolism and detoxification and clearance [147]. Different types of chemotherapy used to treat cancer include alkylating agents, antimetabolites, anti-microtubule agents, topoisomerase inhibitors, antibiotics, and antibodies and all may have a potentially altered efficacy at HA. Anthracyclines (e.g. doxorubicin) or alkylating agents (cisplatin) generate high levels of reactive oxygen species (ROS) that have an impact on cancer cells [149]. Since ROS formation is a tightly balanced process, alterations during cancer therapy may be either tumor promoting (e.g. genetic instability) or inhibiting [150]. Exposure to HA alters the mitochondrial respiratory chain by increasing the COX4-2 expression in a HIF-1 mediated fashion. COX4 is a subunit of cytochrome oxidase and the alternative COX4-2 variant replaces COX4-1 during hypoxia, and so increasing the efficiency of electron transfer in complex IV under low oxygen concentrations [151]. This might prevent excessive ROS formation in cancer cells, but also, as in healthy muscle cells [152, 153], potentially protects organs and tissues from cytotoxic therapies. Furthermore, reduced expression of cytochrome P450 affects the metabolic clearance of drugs [154] and altered blood flow to organs might cause changes in drug distribution in comparison to lowlanders. It is also not clear if HA changes tumor perfusion

and thereby the tumor accessibility of the drugs. The response to tumor therapies at high altitude with and without therapy-associated anemia would be a very interesting area to focus future research efforts.

3.3 Physical Activity

Regular physical activity, either by implementing exercise into daily life activities or by participating in sports, can be considered as an evolutionary based “wonder pill” for humans that has an overall beneficial impact on health throughout life [155, 156]. Fundamental scientific evidence demonstrates that regular physical activity can functionally strengthen and enhance almost every organic system of the human body (e.g. the cardiovascular, respiratory, musculoskeletal, metabolic, neurological, immune, and hematopoietic systems) [157]. Apparently, there is a genetically dependent [158] individual dose response to physical activity that needs to be considered in order to optimize health-related outcomes [159]. On the other hand, a sedentary life style is a well-known risk factor for various diseases and poorer outcomes [160]. In the context of cancer mortality, physical activity is an epidemiologically well-established preventive factor for frequent types of cancers and with a lesser base of evidence, this is true also for other cancers [161, 162]. Furthermore, it is an effective supportive therapeutic strategy during all different phases (pre, during, and post) of cancer therapy even with the potential to lower the risk of cancer reoccurrence [163, 164]. For example, a very recently performed meta-analysis of 26 individual studies found a 37% risk reduction of cancer-specific mortality in the most active patients suffering from either colorectal, breast, or prostate cancer when compared to the least active patients [165]. Considering the previously mentioned aspects of physical activity, it is obvious that the amount of exertion and exercise is a very crucial, if not one of the most important behavioral factors when investigating cancer incidence, prevalence and mortality among populations living at different altitudes. However, in line with a recent review statement by Burtscher *et al.* [48] there is currently a lack of available epidemiological data, which would allow a statistical factorial analysis to evaluate the impact of the level of physical activity, geographical location, and corresponding altitude on cancer-specific mortality. Of note, he recently reported a linear decline of age-standardized mortality rates for male colorectal cancer and female breast cancer with increasing altitude when analyzing data from the Austrian Mortality [166]. The

potentially higher exercise capacity of people living at altitude was proposed, among other factors, to be responsible for the observed lower cancer mortality rate [166]. Driven by the rising socio-economic burden of modern personalized drug-based cancer therapy [167] recent translational efforts across the spectrum from basic to clinical research are beginning to unravel the complex and multifactorial molecular mechanisms responsible for the overall beneficial effects of physical activity on cancer mortality [164]. Obviously, the primary target organs of exercise are the skeletal muscles and heart. Exercise-induced muscle tissue hypoxia may be a key stimulus, predominantly mediated via hypoxia inducible factors (HIFs) signaling cascades [168, 169]. This implicates a complex molecular crosstalk between the two stimuli of physical activity and altitude exposure, which may lead to an altered cellular response in people physically active at altitude. In fact, endurance athletes use various forms of altitude-training (e.g. live high, train high: LHTH) to improve exercise performance by combining both stimuli [170]. In contrast to popular belief, the skeletal musculature is not solely a motor organ but also a highly active endocrine organ that communicates mainly through the vascular circuitry with other body tissues via release of extracellular vesicles and secretory cytokines, known as myokines [171]. A recent preclinical study performed in five different tumor-bearing mouse models found that voluntary exercise on a running-wheel could reduce tumor incidence and growth by more than 60%, especially when applied four weeks before tumor implantation and then continued for the two weeks after tumor implantation [172]. In the same study the authors further reported that these beneficial effects were mainly driven by an epinephrine-dependent mobilization of natural killer cells into the blood stream and interleukin-6 (IL-6)-dependent targeting of these cells to tumors. Interestingly, IL-6 is also a myokine [173], which is known to be secreted from the skeletal muscle upon contraction and probably also hypoxia [174-177]. Another important cellular aspect of physical activity is the fact that exercise can increase the number of adult stem cells (ASCs) [178]. Considering the previously mentioned DeGregori hypothesis of cellular fitness and cancer evolution [47], an exercise-induced increase of healthy ASCs may not only boost tissue regeneration and rejuvenation, but also the anti-oncogenic potential of the corresponding tissue.

To briefly summarize, there is compelling evidence from both animal and human studies that physical activity reduces cancer-specific mortality. However, due to the current lack of

available epidemiological data, no conclusions can be drawn about the impact of physical activity on altered cancer-specific mortality of populations living at different altitudes. Furthermore, the suggested molecular crosstalk between the two stimuli of exercise and altitude exposure further complicates the search for a mechanistic understanding.

4 Conclusion

In many cases, cancer mortality declines with increasing altitude, but the mechanisms that drive tumor suppression are unknown and, due to the complexity of HA adaption processes, difficult to identify. Exposure to HA causes multifactorial cellular, physiological and metabolic alterations that potentially have an impact on tumor mortality. HA and hypoxia induced mechanisms aim at coping with hypoxia and best adapting to HA. Many of these pathways are interconnected in a complex manner. Based on DeGregori's hypothesis of adaptive oncogenesis [47], we suggest that adaptation may increase fitness of healthy cells to better compete with cancer cells within the same niche (Fig.1). In a simplified scheme, one might compare these cells with exercising humans where stress-stimuli increase the cell`s fitness level. As a consequence, it is possible that, instead of individual pathways, the sum of all (or some) adaptive processes results in reduced cancer mortality, which may complicate mechanistically studies. However, some feasible studies could shed some more light on this "black box". The poor prognostic factor anemia of cancer with incidence, pathology, severity and response to treatment could usefully contribute to understanding cancer mortality at HA. The recording of physical activity would be desirable in order to compare the activity pattern of "highlander" and "lowlander" cancer patients in relation to mortality. Finally, the efficacy of drugs including their pharmacodynamics and pharmacokinetics needs to be addressed at HA. Drug metabolism is clearly altered in humans exposed to hypoxia and HA and it is fundamental to understand how patients respond to any kind of drug – including cancer therapeutics – in order to guarantee safety and efficacy.

5 Acknowledgements

The authors kindly thank Jeanne Peter for excellent artwork. We acknowledge the financial support of the Swiss National Science Foundation, Marie-Louise von Muralt Foundation, Krebsliga Switzerland and the Zurich Center for Integrative Human Physiology (ZIHP). We apologize to all those authors whose original or review articles could not be cited due to space limitation.

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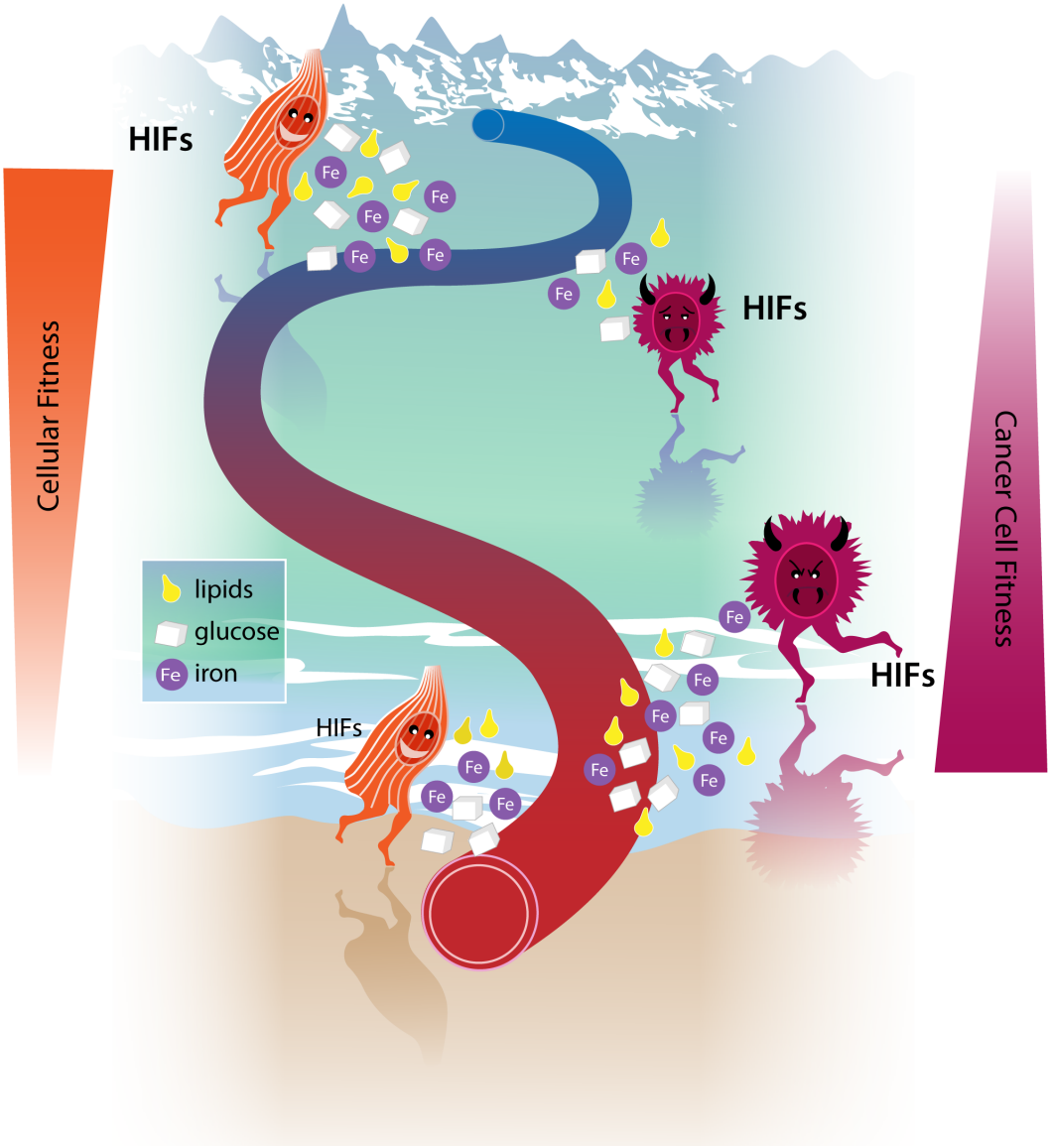

Figure legend:

Figure 1: How high altitude exposure might influence cancer cells.

Assuming that tumorigenesis is an evolutionary selection process, it requires cancer cells (violet) to compete with healthy cells (orange) within the same, resource-restricted niche. If cancer cells are able to successfully populate this niche mainly depends on the quality of the microenvironment (e.g. nutrition availability) and how effective healthy cells are able to compete against cancer cells. In other words, healthy cells with a high cellular fitness as well as an increased demand for nutrition are better competitors and thus impede more successfully the tumor development. Based on this assumption, we suggest a hypothesis for reduced cancer mortality at high altitude: At low altitude (normoxia) expanding tumors increase expression of HIFs that partially contribute to an elevated uptake of lipids, glucose and iron that are essential for tumor progression. Healthy cells in contrast display no increase in HIF-dependent gene expression at low altitude. With increasing altitude however, healthy cells experience a hypoxia-driven, partially HIF-dependent shift in cellular metabolism (similar to tumor cells at low altitude) that may lead to increased nutrition demand. With the activation of nutrition uptake and utilization pathways healthy cells are more competitive, and thus fitter, against cancer cells. Moreover, high altitude exposure leads to a reduction of glucose as well as lipids and potentially iron plasma levels. This suggests that in addition to higher uptake rates of healthy cells the general availability of resources is declining with increasing altitude resulting in unfavorably environmental conditions for tumor growth and thus in a reduction of cancer cell fitness. On top of that, physical activity (e.g. exercise), that is already tumor-suppressive at low altitude may be boosted in combination with HA exposure.